

WHAT IS CLAIMED IS:

1. A purified polynucleotide comprising
 - a) a nucleotide sequence as set forth in SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or SEQ ID NO: 8; or
 - b) a nucleotide sequence encoding a polypeptide having an amino acid sequence as set forth in SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, or SEQ ID NO: 16.
- 10 2. An expression vector comprising the polynucleotide of claim 1.
3. A host cell comprising the expression vector of claim 2.
4. A method of making a modified IL-4 mutein receptor antagonist, comprising
15 the steps of:
 - a) culturing the host cell of claim 3 under conditions whereby the antagonist is expressed; and
 - b) purifying the antagonist from the host cell culture.
- 20 5. A modified IL-4 mutein receptor antagonist produced by the method of claim 4, wherein the antagonist inhibits IL-4 and IL-13-mediated activity.
- 25 6. The modified IL-4 mutein receptor antagonist of claim 5 coupled to a non-protein polymer selected from the group consisting of polyethylene glycol, polypropylene glycol and polyoxyalkylenes.
7. The modified IL-4 mutein receptor antagonist of claim 6 wherein the modified mutein receptor antagonist binds to the IL-4 receptor alpha chain with a K_d of about 0.1 nM to about 10 μ M, about 0.5 nM to about 1 μ M, or about 1.0 nM to about 100 nM.

8. The modified IL-4 mutein receptor antagonist of claim 6 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of TF-1 cells to IL-4 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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9. The modified IL-4 mutein receptor antagonist of claim 6 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of TF-1 cells to IL-13 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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10. The modified IL-4 mutein receptor antagonist of claim 6 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of human B cells to IL-4 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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11. The modified IL-4 mutein receptor antagonist of claim 6 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of human T cells to IL-4 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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12. The modified IL-4 mutein receptor antagonist of claim 6 wherein the modified IL-4 mutein receptor antagonist has a plasma half-life which is at least about 2-10 fold greater than that of an unmodified IL-4 receptor antagonist.

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13. The modified IL-4 mutein receptor antagonist of claim 6 wherein the modified IL-4 mutein receptor antagonist is coupled to the non-protein polymer an amino acid residue at position 28, 36, 37, 38, 104, 105 or 106 of IL-4.

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14. The modified IL-4 mutein receptor antagonist of claim 13 wherein the amino acid residue at position 28, 36, 37, 38, 104, 105 or 106 is cysteine.

15. A method of treating a human disorder associated with increased activity of IL-4 and IL-13, comprising the steps of:

- a) providing a human having a condition in which activity of IL-4 and IL-13 is increased; and
- 5 b) administering to said human an effective amount of modified IL-4 mutein receptor antagonist of claim 6.

16. The method of claim 15 wherein the disorder is asthma, chronic obstructive pulmonary disease, or related pulmonary conditions.

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17. The method of claim 16 wherein the chronic obstructive pulmonary disease is emphysema or chronic bronchitis.

18. A pharmaceutical composition comprising:

15 a) the modified IL-4 mutein receptor antagonist of claim 6; and

- b) a pharmaceutically acceptable carrier.

19. A method of treating a human disorder associated with increased activity of IL-4 and IL-13, comprising the steps of:

20 a) providing a human having a condition in which activity of IL-4 and IL-13 is increased; and

- b) administering to said human an effective amount of the pharmaceutical composition of claim 18.

25 20. The method of claim 19 wherein the disorder is asthma, chronic obstructive pulmonary disease, or related pulmonary conditions.

21. The method of claim 20 wherein the chronic obstructive pulmonary disease is emphysema or chronic bronchitis.

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22. A modified IL-4 mutein receptor antagonist coupled to a non-protein polymer at an amino acid residue at position 28, 36, 37, 38, 104, 105 or 106 of IL-4, wherein the non-protein polymer is polyethylene glycol, polypropylene glycol or a polyoxyalkylene.

5 23. The modified IL-4 mutein receptor antagonist of claim 22 comprising an amino acid sequence as set forth in SEQ ID NO: 10.

24. The modified IL-4 mutein receptor antagonist of claim 22 comprising an amino acid sequence as set forth in SEQ ID NO: 11.

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25. The modified IL-4 mutein receptor antagonist of claim 22 comprising an amino acid sequence as set forth in SEQ ID NO: 12.

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26. The modified IL-4 mutein receptor antagonist of claim 22 comprising an amino acid sequence as set forth in SEQ ID NO: 13.

27. The modified IL-4 mutein receptor antagonist of claim 22 comprising an amino acid sequence as set forth in SEQ ID NO: 14.

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28. The modified IL-4 mutein receptor antagonist of claim 22 comprising an amino acid sequence as set forth in SEQ ID NO: 15.

29. The modified IL-4 mutein receptor antagonist of claim 22 comprising an amino acid sequence as set forth in SEQ ID NO: 16.

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30. The modified IL-4 mutein receptor antagonist of claim 22 wherein the modified mutein receptor antagonist binds to the IL-4 receptor alpha chain with a K_d of about 0.1 nM to about 10 μ M, about 0.5 nM to about 1 μ M, or about 1.0 nM to about 100 nM.

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31. The modified IL-4 mutein receptor antagonist of claim 22 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of TF-1 cells to IL-4 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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32. The modified IL-4 mutein receptor antagonist of claim 22 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of TF-1 cells to IL-13 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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33. The modified IL-4 mutein receptor antagonist of claim 22 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of human B cells to IL-4 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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34. The modified IL-4 mutein receptor antagonist of claim 22 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of human T cells to IL-4 with an IC₅₀ of about 0.1 nM to about 10 µM, about 0.5 nM to about 1 µM, or about 1.0 nM to about 100 nM.

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35. The modified IL-4 mutein receptor antagonist of claim 22 wherein the modified IL-4 mutein receptor antagonist has a plasma half-life which is at least about 2-10 fold greater than that of an unmodified IL-4 receptor antagonist.

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36. The modified IL-4 mutein receptor antagonist of claim 22 wherein the amino acid residue at position 28, 36, 37, 38, 104, 105 or 106 is cysteine.

37. A pharmaceutical composition comprising:

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- a) the modified IL-4 mutein receptor antagonist of claim 22; and
- b) a pharmaceutically acceptable carrier.

38. A method of treating a human disorder associated with increased activity of IL-4 and IL-13, comprising the steps of:

- a) providing a human having a condition in which activity of IL-4 and IL-13 is increased; and
- 5 b) administering to said human an effective amount of the pharmaceutical composition of claim 37.

39. The method of claim 38 wherein the disorder is asthma, chronic obstructive pulmonary disease, or related pulmonary conditions.

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40. The method of claim 39 wherein the chronic obstructive pulmonary disease is emphysema or chronic bronchitis.

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41. A method of making a modified IL-4 mutein receptor antagonist in active form, comprising the steps of:

- a) culturing the host cell of claim 3 under conditions whereby the antagonist is expressed;
- b) allowing the antagonist to refold in the presence of dithiothreitol; and
- c) purifying the antagonist from the host cell culture.

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42. The method of claim 41, further comprising the steps of:

- d) coupling the antagonist to a non-protein polymer; and
- e) purifying the antagonist coupled to the non-protein polymer.

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43. A modified IL-4 mutein receptor antagonist produced by the method of claims 41 or 42, wherein the antagonist inhibits IL-4 and IL-13-mediated activity.

44. The modified IL-4 mutein receptor antagonist of claim 43 wherein the non-protein polymer is polyethylene glycol, polypropylene glycol or a polyoxyalkylene.

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45. The modified IL-4 mutein receptor antagonist of claim 44 wherein the modified mutein receptor antagonist binds to the IL-4 receptor alpha chain with a K_d of about 0.1 nM to about 10 μ M, about 0.5 nM to about 1 μ M, or about 1.0 nM to about 100 nM.

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46. The modified IL-4 mutein receptor antagonist of claim 44 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of TF-1 cells to IL-4 with an IC_{50} of about 0.1 nM to about 10 μ M, about 0.5 nM to about 1 μ M, or about 1.0 nM to about 100 nM.

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47. The modified IL-4 mutein receptor antagonist of claim 44 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of TF-1 cells to IL-13 with an IC_{50} of about 0.1 nM to about 10 μ M, about 0.5 nM to about 1 μ M, or about 1.0 nM to about 100 nM.

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48. The modified IL-4 mutein receptor antagonist of claim 44 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of human B cells to IL-4 with an IC_{50} of about 0.1 nM to about 10 μ M, about 0.5 nM to about 1 μ M, or about 1.0 nM to about 100 nM.

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49. The modified IL-4 mutein receptor antagonist of claim 44 wherein the modified IL-4 mutein receptor antagonist inhibits the proliferative response of human T cells to IL-4 with an IC_{50} of about 0.1 nM to about 10 μ M, about 0.5 nM to about 1 μ M, or about 1.0 nM to about 100 nM.

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50. The modified IL-4 mutein receptor antagonist of claim 44 wherein the modified IL-4 mutein receptor antagonist has a plasma half-life which is at least about 2-10 fold greater than that of an unmodified IL-4 receptor antagonist.

51. The modified IL-4 mutein receptor antagonist of claim 44 wherein the modified IL-4 mutein receptor antagonist is coupled to the non-protein polymer an amino acid residue at position 28, 36, 37, 38, 104, 105 or 106 of IL-4.

5 52. The modified IL-4 mutein receptor antagonist of claim 51 wherein the amino acid residue at position 28, 36, 37, 38, 104, 105 or 106 is cysteine.

53. A method of treating a human disorder associated with increased activity of IL-4 and IL-13, comprising the steps of:

10 a) providing a human having a condition in which activity of IL-4 and IL-13 is increased; and

b) administering to said human an effective amount of modified IL-4 mutein receptor antagonist of claim 44.

15 54. The method of claim 53 wherein the disorder is asthma, chronic obstructive pulmonary disease, or related pulmonary conditions.

55. The method of claim 54 wherein the chronic obstructive pulmonary disease is emphysema or chronic bronchitis.

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56. A pharmaceutical composition comprising:

- a) the modified IL-4 mutein receptor antagonist of claim 43; and
- b) a pharmaceutically acceptable carrier.

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57. A method of treating a human disorder associated with increased activity of IL-4 and IL-13, comprising the steps of:

a) providing a human having a condition in which activity of IL-4 and IL-13 is increased; and

30 b) administering to said human an effective amount of the pharmaceutical composition of claim 56.

58. The method of claim 57 wherein the disorder is asthma, chronic obstructive pulmonary disease, or related pulmonary conditions.
59. The method of claim 58 wherein the chronic obstructive pulmonary disease is
5 emphysema or chronic bronchitis.